REMARKS

Claims 1-8 are currently pending in the instant application. Claims 1, 2, and 6 have been amended to correct minor typographical and formatting errors. Claim 1 has been amended to recite "X denotes a nitrogen atom". Support for the recitation of a method of treating a malignant tumour "wherein the malignant tumour is of epithelial or neuroepithelial origin" of claim 7 can be found throughout the specification, *inter alia*, page 20, paragraph 1. Support for the recitation of a method of treating a disease of the respiratory tract or lungs which is accompanied by increased or altered production of mucus caused by stimulation of tyrosine kinases of claim 8 can be found throughout the specification and claims as originally filed, *inter alia*, at page 20, paragraph 2.

No new matter has been added. In light of the above amendments, claims 1-8 are under active consideration in this application.

Claim Objections-Election/Restrictions

Claims 1 and 5-7 are objected to as being drawn to an improper Markush group. Claim 1 has been amend to recite a compound where X is a nitrogen atom. This objection, therefore, has been obviated.

Section 112, First Paragraph Rejections

Claims 6 and 7 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement.

The Examiner contends that the scope of the method claims 6 and 7 are not enabled solely based on its tyrosine kinase inhibition provided in the specification.

As a preliminary matter, Applicants point out that claim 6 is directed to a pharmaceutical composition, not to a method of treating a disease. Thus, this rejection with regard to claim 6 is moot.

Claim 7, as now amended, is directed to a method of treating a malignant tumour, comprising administering a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, wherein the malignant tumour is of epithelial or neuroepithelial origin. Claim 8 is directed to a method of treating a disease of the respiratory

tract or lungs, which comprises administering a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, wherein the disease of the respiratory tract or lungs is accompanied by increased or altered production of mucus caused by stimulation of tyrosine kinases, and wherein the disease of the respiratory tract or lungs is selected from the group consisting of: chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasias, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways.

Applicants disagree with the rejection of claim 7 (now claims 7 and 8) both as a matter of fact and law. The Examiner relies on *In re Buting*, 163 USPQ 689, which was decided in 1969.

An invention meets the standard for successful practice set by Section 112 unless the invention is "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 24 USPQ 2D 1401, 1412 (Fed. Cir. 1992). The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 USPQ 2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, first paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents.

The Federal Circuit emphatically reversed the Board's decision and explained that the legal standard for compliance with the relevant Section 112 requirement is that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* At 1441 (emphasis in original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence.

Applicants direct the Examiner's attention to Boschelli, D.H., Small molecule inhibitors of receptor tyrosine kinases, Review Article. Chemical Sciences, Drugs of the Future, 1999, 24(5):515-537 ("Boschelli"), previously submitted in an Information

Disclosure Statement on October 21, 2001. Boschelli describes the role of tyrosine kinases, for example, on the epidermal growth factor rector (EGF-R) family, the implication of EGF in the development and progression of cancer, and the use of inhibitors of tyrosine kinase activity for the treatment of various cancers (pages 1-12). Applicants also direct the Examiner's attention to U.S. Patent No. 6,566,324, submitted herewith, wherein a method for treating hypersecretion of mucus in lungs by administration of an epidermal growth factor receptor (EGF-R) antagonist is described throughout the specification and claims. The Examiner's attention is also directed to the specification, pages 18-20, wherein Applicants have provided an example demonstrating inhibition of the EGF-R-mediated signal transmission by compounds of general formula I.

Applicants maintain that for the reasons set forth above, *e.g.*, inhibition of the EGF-R-mediated signal transmission, the given compounds are useful for treating various malignant tumors of epithelial or neuroepithelial origin (claim 7 , as amended) as well as for treating a disease of the respiratory tract or lungs, wherein the disease of the respiratory tract or lungs is accompanied by increased or altered production of mucus caused by stimulation of tyrosine kinases, and wherein the disease of the respiratory tract or lungs is selected from the group consisting of: chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasias, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways (claim 8).

Thus, Applicants submit that the indication for treating a disease of the respiratory tract and lungs, as well as for treating a malignant tumor, is fully enabled.

In light of the above amendments and remarks, it is submitted that this rejection under Section 112 has been overcome and must be withdrawn.

Section 112, Second Paragraph Rejections

Claims 1-3 and 5-7 are rejected under 35 U.S.C §112, second paragraph as being indefinite.

According to the Examiner, claims 1-3 and 5-7 are vague and indefinite in that it is not know what is meant by the second occurrence of the structure of Formula I.

Applicants submit that the second occurrence of the structure of Formula I was a typographical error. The second occurrence of the structure of Formula I has been deleted; thereby obviating this rejection.

According to the Examiner, claims 1 and 5-7 are vague and indefinite in that it is not know what is meant by the two different definitions for the variable Y.

Applicants submit that claim 1 (and claims 2, 3, and 5-7, dependent thereon) inadvertently contained various formatting errors which have been corrected by this amendment. Claim 1, as presently amended, now makes it clear that the paragraph of lines 25 and 26 on page 52 must be read together with the paragraph above. There are not two different definitions for the variable Y; thus this rejection is moot.

The Examiner contends that there is insufficient antecedent basis for the limitation "substituted in the 4-position by a R6S group" in the substituent on the piperidino group in line 21 of page 54.

Applicant submit that the cited limitation has antecedent basis in claim 1:

"a pyrrolidino, piperidino or hexahydroazepino group substituted by the group R_6, wherein

R_6 denotes a 2-oxo-tetrahydrofuranyl, 2-oxo-tetrahydropyranyl, 2-oxo-1,4-dioxanyl or 2-oxo-4-(C_{1-4}-alkyl)-morpholinyl group optionally substituted by one or two C_{1-2}-alkyl groups,"

Applicants submit that since no position is given for the substitution in claim 1, any possible position is included in the definition. Thus, this rejection should be withdrawn.

According to the Examiner, claim 7 is vague and indefinite in that the claim provides for the use of claimed compounds, but does not set forth any steps involved in determining which are the diseases capable of being modulated by inhibiting the catalytic activity of tyrosine kinase. The Examiner further contends that determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation.

Applicants emphatically disagree with this rejection. Claim 7, as now amended, is directed to a method of treating a malignant tumour, comprising administering a therapeutically effective amount of a compound of the invention or a pharmaceutically

acceptable salt thereof, *wherein the malignant tumour is of epithelial or neuroepithelial origin*. Claim 8 is directed to a method of treating a disease of the respiratory tract or lungs, which comprises administering a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, *wherein the disease of the respiratory tract or lungs is accompanied by increased or altered production of mucus caused by stimulation of tyrosine kinases, and wherein the disease of the respiratory tract or lungs is selected from the group consisting of: chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasias, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways*.

A decision as to whether a claim is invalid for indefiniteness under Section 112 requires a determination whether those skilled in the art would understand what is claimed. Claims must reasonably apprise those skilled in the art as to their scope and be as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985). Accordingly, Applicants respectfully submit that one skilled in the art would have no problem understanding what is being claimed.

With regard to the Examiner's contentions that the invention would involve undue experimentation, these matters have rightly been addressed above in relation to enablement under Section 112, first paragraph. Further, Applicants point out that dosage ranges and regimens are described in the specification at pages 21-22. Applicants also emphasize that, as will be apparent to the skilled practitioner, for administration of the claimed compositions according to the invention, the exact formulation, route of administration and dosage can and should be chosen by the individual physician in view of the patient's condition (*i.e.*, extent of disease, general age, health, etc.). Any experimentation need to ascertain proper dosage levels in a given situation would not be undue, but rather would lie well within the ability of one of ordinary skill in the art. *In re Bundy*, 209 USPQ 48 (CCPA 1981) (addressing sufficiency under Section 112 of disclosure regarding pharmacologic use of claimed compound); *In re Hitchings, Elion & Goodman*, 144 USPQ 637 (CCPA 1965) (addressing sufficiency under Section 112 of disclosure regarding anti-cancer chemotherapeutic use of claimed compound).

In light of the above amendments and remarks, Applicants submit that all of the rejections under Section 112, second paragraph have been obviated and must be withdrawn.

Double Patenting

Claims 1, 2 and 5-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of co-pending U.S. Patent 6,403,580.

In response, Attorney for Applicants files herewith a Terminal Disclaimer to obviate a Double Patenting Rejection over a Prior Patent.

Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of co-pending U.S. Application No. 09/914,323.

In response, Attorney for Applicants files herewith a Terminal Disclaimer to obviate a Provisional Double Patenting Rejection over a Pending Patent Application.

In light of the Terminal Disclaimers, all of the rejections for double patenting have been obviated and must be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that all of the objections and rejections have been overcome and must be withdrawn. Further, Applicants submit that the application is now in form for issuance and an early allowance is earnestly requested. If any issues remain, the Examiner is invited to telephone the Attorney at the number listed below.

Respectfully submitted,

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